

CLAIMS

1. A pharmaceutical composition active against HIV comprising as an active ingredient a linked cyclic compound of (general) formula I,



in which Z and (in) Y are identical cyclic polyamine moieties having from 9 to 20 (ring members) and from 3 to 6 amine nitrogens in the ring spaced by 2 or more carbon atoms from each other,

A is an aromatic or heteroaromatic moiety other than quinoline,

R and R' are each methylene linked to nitrogen atoms in Z and Y, the amine nitrogen atoms being otherwise unsubstituted,

or a non-toxic acid addition salt or metal complex thereof, in admixture or association with a pharmaceutically acceptable diluent or carrier.

✓ 2. A composition according to claim 1, wherein, in the compound of formula I, each moiety Z and Y has 10 to 15 ring members.

23. A composition according to claim 1, wherein in the compound of formula I, each moiety Z and Y has 14 ring members and 4 amine nitrogens in the ring.

SUBSTITUTE SHEET

- 3/4. A composition according to claim 1, wherein the active ingredient is 1,1'-[1,3-phenylenebis (methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane in acid addition salt form.
- 5 4/5. A composition according to claim 1, wherein the active ingredient is 1,1'-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane in acid addition salt form.
- 10 5/6. A composition according to claim 1, wherein the active ingredient is a bis-zinc complex of 1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane.
- 15 6/7. A composition according to claim 1, wherein the active ingredient is a bis-copper complex of 1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane.
- 20 7/8. A composition according to claim 1, wherein the active ingredient is 1,1'-[3,3'-biphenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.
- 4/9. A composition according to claim 1, wherein the active ingredient is 11,11'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,11-tetraazacyclotetradecane in acid addition salt form.

SUBSTITUTE SHEET

49

9. ~~10.~~ A composition according to claim 1, wherein the active ingredient is 1,11'-[1,4-phenylene-bis-(methylene)]-1,4,8,11-tetraazacyclotetradecane-1,4,7,11-tetraazacyclotetradecane in acid addition salt form.

5 ~~10.~~ ¹⁰ 11. A composition according to claim 1, wherein the active ingredient is 1,1'-[2,6-pyridine-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.

~~11.~~ ¹¹ 12. A composition according to claim 1, wherein the active ingredient is 1,1-[3,5-pyridine-bis-(methylene)]-bis-1,4,8,11-tetraazacyclo tetradecane in acid addition salt form.

~~12.~~ ¹² 13. A composition according to claim 1, wherein the active ingredient is 1,1'-[2,5-thiophene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.

~~13.~~ ¹³ 14. A composition according to claim 1, wherein the active ingredient is 1,1'-[4,4'-(2,2'-bipyridine)-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.

20 ~~14.~~ ¹⁴ 15. A composition according to claim 1, wherein the active ingredient is 1,1'-[2,9-(1,10-phenanthroline)-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.

SUBSTITUTE SHEET

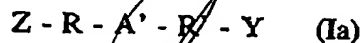
60

16. A composition according to claim 1, wherein the active ingredient is 1,1'-[1,3-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane in acid addition salt form.

17. A composition according to claim 1, wherein the active ingredient is 1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane in acid addition salt form.

18. A composition according to any one of the preceding claims, in unit dosage form.

✓ 19. A linked cyclic compound of formula Ia,



wherein Z, Y, R and R' are as defined in claim 1, and A' is an aromatic or heteroaromatic moiety which is unsubstituted or substituted, other than quinoline, and its addition salts and metal complexes, other than the base in which A' is unsubstituted phenylene when Z and Y are 14-membered tetraaza rings.

✓ 20. A compound according to claim 19, wherein A' is substituted or unsubstituted phenylene or substituted or unsubstituted naphthylene.

21. The compound of claim ¹19, which is 1,1'-[5-nitro-1,3-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.

5 22. The compound of claim ¹19, which is 1,1'-[2,4,5,6-tetrachloro-1,3-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.

10 23. The compound of claim ¹19, which is 1,1'-[2,3,5,6-tetra-fluoro-1,4-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.

15 24. The compound of claim ¹19, which is 1,1'-[1,4-naphthylene-bis-(methylene)]bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.

20 25. The compound of claim ¹19, which is 1,1'-[1,3-phenylenebis-(methylene)]bis-1,5,9-triazacyclododecane in acid addition salt form.

20 26. The compound of claim ¹19, which is 1,1'-[1,4-phenylene-bis-(methylene)]-1,5,9-triazacyclododecane in acid addition salt form.

23 27. The compound of claim ¹19, which is a bis-zinc complex of 1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane.

SUBSTITUTE SHEET

28. The compound of claim 19, which is a bis-copper complex of 1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane.

24

29. The compound of claim 19, which is 1,1'-[3,3'-biphenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.

30. The compound of claim 19, which is 11,11'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,11-tetraazacyclotetradecane in acid addition salt form.

25

31. The compound of claim 19, which is 1,1'-[2,6-pyridine-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.

26

32. The compound of claim 19, which is 1,1'-[3,5-pyridine-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.

27

33. The compound of claim 19, which is 1,1'-[2,5-thiophene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.

28

34. The compound of claim 19, which is 1,1'-[4,4'-(2,2'-bipyridine)-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.

29

35. The compound of claim 19, which is 1,1'-[2,9-(1,10-phenanthroline)-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane in acid addition salt form.

SUBSTITUTE SHEET

30
36.

The compound of claim 19, which is 1,1'-[1,3-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane in acid addition salt form.

31
37.

The compound of claim 19, which is 1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane in acid addition salt form.

32
38.

The compound of claim 19, which is 1,1'-[2,5-dimethyl-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane.

33
39.

The compound of claim 19, which is 1,1'-[2,5-dichloro-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane.

34
40.

The compound of claim 19, which is 1,1'-[2-bromo-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane.

35
41.

The compound of claim 19, which is 1,1'-[6-phenyl-2,4-pyridinebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane.

42. A method for the production of a compound according to claim 19, comprising nucleophilic attack by cyclic polyamines Z' and Y' each being a polyamine Z or Y as defined in claim 1 and having a single unprotected ring amine nitrogen, all other ring amine nitrogens being protected, on a compound of formula II,



wherein R, R' and A' are as defined in claims 1 and 10 respectively, and

X is an active substituent which can be displaced by the unprotected amine nitrogens of polyamines Z' and Y',

5 and subsequently deprotecting the ring amine nitrogens.

43. A method according to claim 42, wherein the substitution takes place in the presence of a solvent and in the presence of a base.

10 44. A method according to claim 42 or 43, wherein the nitrogen atoms of the cyclic polyamines are protected by methanesulfonyl and/or 4-tolylsulfonyl and/or diethylphosphoryl.

15 45. A method according to claim 42, 43 or 44, wherein the deprotection is carried out in a mixture of HBr and acetic acid in the case of methanesulfonyl and 4-tolylsulfonyl protection or by HCl in THF or dioxane in the case of diethylphosphoryl protection.